L Number	Hits	Search Text	DB	Time stamp
1	230	phosphoinositide adj "3" adj kinase	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/27 12:45
2	2	(phosphoinositide adj "3" adj kinase) near3 crystal	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/27 12:45

L Number	Hits	Search Text	DB	Time stamp
1	0	(phosphatidylinositol adj "3" adj kinase) near5 crystal	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/27 14:11

```
Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:ssspta1653sxs

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  CA/CAplus records now contain indexing from 1907 to the
                  present
 NEWS  4  DEC 08  INPADOC: Legal Status data reloaded
 NEWS  5  SEP 29  DISSABS now available on STN
 NEWS  6  OCT 10  PCTFULL: Two new display fields added
 NEWS  7  OCT 21  BIOSIS file reloaded and enhanced
 NEWS  8  OCT 28  BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9  NOV 24  MSDS-CCOHS file reloaded
 NEWS 10  DEC 08  CABA reloaded with left truncation
 NEWS 11  DEC 08  IMS file names changed
 NEWS 12  DEC 09  Experimental property data collected by CAS now available
                  in REGISTRY
 NEWS 13  DEC 09  STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14  DEC 17  DGENE: Two new display fields added
 NEWS 15  DEC 18  BIOTECHNO no longer updated
 NEWS 16  DEC 19  CROPU no longer updated; subscriber discount no longer
                  available
 NEWS 17  DEC 22  Additional INPI reactions and pre-1907 documents added to CAS
                  databases
 NEWS 18  DEC 22  IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19  DEC 22  ABI-INFORM now available on STN
 NEWS 20  JAN 27  Source of Registration (SR) information in REGISTRY updated
                  and searchable
 NEWS 21  JAN 27  A new search aid, the Company Name Thesaurus, available in
                  CA/CAplus
 NEWS 22  FEB 05  German (DE) application and patent publication number format
                  changes

 NEWS EXPRESS  DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.
```

```
  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:55:58 ON 27 FEB 2004

=> File bioscience health medicine meetings pharmacology research toxicology
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'ADISCTI' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Adis Data Information BV

FILE 'ADISINSIGHT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Adis Data Information BV

FILE 'ADISNEWS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Adis Data Information BV

FILE 'AGRICOLA' ENTERED AT 12:56:07 ON 27 FEB 2004

FILE 'ANABSTR' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 THE ROYAL SOCIETY OF CHEMISTRY (RSC)

FILE 'AQUASCI' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT 2004 FAO (On behalf of the ASFA Advisory Board). All rights reserved.

FILE 'BIOBUSINESS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Biological Abstracts, Inc. (BIOSIS)

FILE 'BIOCOMMERCE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 BioCommerce Data Ltd. Richmond Surrey, United Kingdom. All
rights reserved

FILE 'BIOSIS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'BIOTECHABS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT AND INSTITUTE FOR SCIENTIFIC INFORMATION

FILE 'BIOTECHDS' ACCESS NOT AUTHORIZED

FILE 'BIOTECHNO' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'CABA' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 CAB INTERNATIONAL (CABI)

FILE 'CANCERLIT' ENTERED AT 12:56:07 ON 27 FEB 2004

FILE 'CAPLUS' ENTERED AT 12:56:07 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'CEABA-VTB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 DECHEMA eV

FILE 'CEN' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 American Chemical Society (ACS)

FILE 'CIN' ENTERED AT 12:56:07 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
```

COPYRIGHT (C) 2004 American Chemical Society (ACS)

FILE 'CONFSCI' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'CROPB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'CROPU' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'DISSABS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 ProQuest Information and Learning Company; All Rights Reserved.

FILE 'DDFB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'DDFU' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'DGENE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'DRUGB' ACCESS NOT AUTHORIZED

FILE 'DRUGMONOG2' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 IMSWORLD Publications Ltd

FILE 'IMSDRUGNEWS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 IMSWORLD Publications Ltd

FILE 'DRUGU' ACCESS NOT AUTHORIZED

FILE 'IMSRESEARCH' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 IMSWORLD Publications Ltd

FILE 'EMBAL' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE 'EMBASE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE 'ESBIOBASE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'FEDRIP' ENTERED AT 12:56:07 ON 27 FEB 2004

FILE 'FOMAD' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Leatherhead Food Research Association

FILE 'FOREGE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Leatherhead Food Research Association

FILE 'FROSTI' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Leatherhead Food Research Association

FILE 'FSTA' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 International Food Information Service

FILE 'GENBANK' ENTERED AT 12:56:07 ON 27 FEB 2004

FILE 'HEALSAFE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'IFIPAT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 IFI CLAIMS(R) Patent Services (IFI)

FILE 'IMSPRODUCT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 IMSWORLD Publications Ltd

FILE 'JICST-EPLUS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Japan Science and Technology Agency (JST)

FILE 'KOSMET' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 International Federation of the Societies of Cosmetics Chemists

FILE 'LIFESCI' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'MEDICONF' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 FAIRBASE Datenbank GmbH, Hannover, Germany

FILE 'MEDLINE' ENTERED AT 12:56:07 ON 27 FEB 2004

FILE 'NIOSHTIC' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 U.S. Secretary of Commerce on Behalf of the U.S. Government

FILE 'NTIS' ENTERED AT 12:56:07 ON 27 FEB 2004
Compiled and distributed by the NTIS, U.S. Department of Commerce.
It contains copyrighted material.
All rights reserved. (2004)

FILE 'NUTRACEUT' ENTERED AT 12:56:07 ON 27 FEB 2004
Copyright 2004 (c) MARKETLETTER Publications Ltd. All rights reserved.

FILE 'OCEAN' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'PASCAL' ENTERED AT 12:56:07 ON 27 FEB 2004
Any reproduction or dissemination in part or in full,
by means of any process and on any support whatsoever
is prohibited without the prior written agreement of INIST-CNRS.
COPYRIGHT (C) 2004 INIST-CNRS. All rights reserved.

FILE 'PCTGEN' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 WIPO

FILE 'PHAR' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 PJB Publications Ltd. (PJB)

FILE 'PHARMAML' ENTERED AT 12:56:07 ON 27 FEB 2004
Copyright 2004 (c) MARKETLETTER Publications Ltd. All rights reserved.

FILE 'PHIC' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 PJB Publications Ltd. (PJB)

FILE 'PHIN' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 PJB Publications Ltd. (PJB)

FILE 'PROMT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Gale Group. All rights reserved.

FILE 'RDISCLOSURE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Kenneth Mason Publications Ltd.

FILE 'SCISEARCH' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT 2004 THOMSON ISI

FILE 'SYNTHLINE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Prous Science

FILE 'TOXCENTER' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 ACS

FILE 'USPATFULL' ENTERED AT 12:56:07 ON 27 FEB 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 12:56:07 ON 27 FEB 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'VETB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'VETU' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'WPIDS' ACCESS NOT AUTHORIZED

FILE 'WPINDEX' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'ABI-INFORM' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 ProQuest Information and Learning Company; All Rights Reserved.

FILE 'CBNB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 ELSEVIER ENGINEERING INFORMATION, INC.

FILE 'CHEMLIST' ENTERED AT 12:56:07 ON 27 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

FILE 'CSNB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 THE ROYAL SOCIETY OF CHEMISTRY (RSC)

FILE 'ENERGY' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 USDOE for the IEA-Energy Technology Data Exchange (ETDE)

FILE 'HSDB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 NATIONAL LIBRARY OF MEDICINE

FILE 'INIS' ACCESS NOT AUTHORIZED

FILE 'IPA' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 American Society of Hospital Pharmacists (ASHP)

FILE 'MSDS-CCOHS' ENTERED AT 12:56:07 ON 27 FEB 2004
Copyright Notice: Permission to copy is not required for this file

FILE 'MSDS-OHS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 MDL INFORMATION SYSTEMS (MDL)

FILE 'NAPRALERT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Board of Trustees of the University of Illinois,
University of Illinois at Chicago.

FILE 'NLDB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Gale Group. All rights reserved.

FILE 'POLLUAB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'RTECS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 U.S. Secretary of Commerce on Behalf of the U.S. Government (DOC)

FILE '1MOBILITY' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Society of Automotive Engineers, Inc.

FILE 'COMPENDEX' ENTERED AT 12:56:07 ON 27 FEB 2004
Compendex Compilation and Indexing (C) 2004
Elsevier Engineering Information Inc (EEI). All rights reserved.
Compendex (R) is a registered Trademark of Elsevier Engineering Information Inc.

FILE 'COMPUAB' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'CONF' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 FIZ Karlsruhe

FILE 'ELCOM' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'IMSDRUGCONF' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 IMSWORLD Publications Ltd.

FILE 'PAPERCHEM2' ENTERED AT 12:56:07 ON 27 FEB 2004
Paperchem2 compilation and indexing (C) 2004
Elsevier Engineering Information Inc. All rights reserved.

FILE 'SOLIDSTATE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE 'BABS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (c) 2004 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften
licensed to Beilstein GmbH and MDL Information Systems GmbH

FILE 'DIOGENES' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 FOI Services, Inc. (FOI)

FILE 'INVESTEXT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Thomson Financial Services, Inc. (TFS)

FILE 'USAN' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 U.S. Pharmacopeial Convention, Inc. (USPC)

FILE 'DKF' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Dokumentation Kraftfahrwesen e.V., Germany

FILE 'FORIS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Informationszentrum Sozialwissenschaften, Bonn (IZS)

FILE 'FORKAT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Bundesministerium fuer Bildung,
Wissenschaft, Forschung und Technologie (bmb+f)

FILE 'RUSSCI' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Inputmax Ltd.

FILE 'SOLIS' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Informationszentrum Sozialwissenschaften, Bonn (IZS)

```
FILE 'UFORDAT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Umweltbundesamt, D-14191 Berlin (UBA)

FILE 'AQUIRE' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 US Environmental Protection Agency (EPA)

FILE 'ULIDAT' ENTERED AT 12:56:07 ON 27 FEB 2004
COPYRIGHT (C) 2004 Umweltbundesamt, D-14191 Berlin (UBA)

=> s phosphoinositide (w) 3 (w) kinase
  24 FILES SEARCHED...
  49 FILES SEARCHED...
  75 FILES SEARCHED...
L1       14762 PHOSPHOINOSITIDE (W) 3 (W) KINASE

=> s l1 (3A) crystal
  46 FILES SEARCHED...
  79 FILES SEARCHED...
L2          10 L1 (3A) CRYSTAL

=> duplicate
ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove
ENTER L# LIST OR (END):l2
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, BIOCOMMERCE, DGENE,
DRUGMONOG2, IMSRESEARCH, FEDRIP, FOREGE, GENBANK, IMSPRODUCT, KOSMET,
MEDICONF, NUTRACEUT, PCTGEN, PHAR, PHARMAML, RDISCLOSURE, SYNTHLINE, CHEMLIST,
HSDB, MSDS-CCOHS, MSDS-OHS, RTECS, CONF, IMSDRUGCONF, DIOGENES, INVESTEXT,
USAN, FORIS, FORKAT, UFORDAT, AQUIRE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
DUPLICATE PREFERENCE IS 'BIOTECHABS, CAPLUS, DGENE, TOXCENTER, WPINDEX'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L2
L3            7 DUPLICATE REMOVE L2 (3 DUPLICATES REMOVED)

=> s l3 NOT (complete genome)
  14 FILES SEARCHED...
  35 FILES SEARCHED...
  56 FILES SEARCHED...
  82 FILES SEARCHED...
L4           7 L3 NOT (COMPLETE GENOME)

=> d l4 1-7 bib ab

L4    ANSWER 1 OF 7  BIOTECHABS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN    2003-16725  BIOTECHABS
TI    New phosphoinositide 3-kinase gamma (PI3K
      gamma) crystals, polypeptide fragments and muteins, useful for
      modifying PI3K gamma activity, e.g. for regulating cellular activities
      involved in inflammation, repair, or healing;
         involving vector-mediated gene transfer and expression in host cell
         for use in cancer, inflammation and vulnerary therapy
AU    WILLIAMS R; RIED C; WALKER E H; STEPHENS L
PA    WILLIAMS R; RIED C; WALKER E H; STEPHENS L
PI    US 2003022344 30 Jan 2003
AI    US 2001-974573 9 Oct 2001
PRAI  US 2001-974573 9 Oct 2001; US 2000-242801 23 Oct 2000
DT    Patent
LA    English
OS    WPI: 2003-416991 [39]
AB    DERWENT ABSTRACT:
      NOVELTY - A phosphoinositide 3-kinasegamma crystal is new.
           DETAILED DESCRIPTION - The phosphoinositide 3-kinasegamma
      (PI3Kgamma) crystal has a unit dimension of: a  =  143.3 Angstrom; b  =
```

67.6 Angstrom; c = 107 Angstrom; and beta = 95.9 Angstrom.
INDEPENDENT CLAIMS are also included for the following: (1) modulating phospholipid substrate binding to PI3Kgamma comprising modifying the phospholipid domain of PI3Kgamma, which comprises the C-terminal helix kalpha12, catalytic loop, and activation loop; (2) isolated polypeptide fragment of PI3Kgamma consisting essentially of: (a) a phospholipid binding domain, which comprises the C-terminal helix kalpha12, catalytic loop, and activation loop; (b) the kbeta1-kbeta2, kbeta4-kbeta5, kalpha6, Ralpha2, and Rbeta3-Rbeta4 domains of PI3Kgamma; (c) the lining of the crevice region between the N- and C-lobes, the CBR regions, or the region comprising the tip of the activation loop; or (d) hB1-hB5; (3) isolated polypeptide mutein of PI3Kgamma comprising: (a) a phospholipid binding domain, which comprises the C-terminal helix kalpha12, catalytic loop, and activation loop of a dully defined sequence of 1102 amino acids (I) given in the specification, and at least 95% sequence identity to the remaining sequence of (I); (b) a sequence having at least 95% amino acid sequence identity to (I) and having His968; (c) the kbeta1-kbeta2, kbeta4-kbeta5, kalpha6, Ralpha2, and Rbeta3-Rbeta4 domains, Lys234, Asp238 and Lys255 of the sequence of (I), and at least 95% sequence identity to the remaining sequence of (I); (d) the lining of the crevice region between the N- and C-lobes, the CBR regions, or the region comprising the tip of the activation loop of the amino acid sequence of (I), and at least 95% sequence identity to the remaining sequence of (I); or (e) hB1-hB5 of the amino acid sequence of (I), and at least 95% sequence identity to the remaining sequence of (I); (4) isolated polypeptide of a PI3Kgamma consisting essentially of 8-100 amino acids, comprising His968; (5) antibody that is specific for the phospholipid binding domain or any of the polypeptides cited above; (6) nucleic acid coding for any of the polypeptides above; (7) modulating lipid kinase catalysis comprising modifying His968 of a PI3Kgamma; (8) modulating RAS activity in activating PI3Kgamma comprising modifying the kbeta1-kbeta2, kbeta4-kbeta5, kalpha6, Ralpha2, and Rbeta3-Rbeta4 domains of PI3Kgamma; (9) inhibiting the binding of PI3Kgamma to cell membranes comprising modifying the lining of the crevice region between the N- and C-lobes, the CBR regions, or the region comprising the tip of the activation loop, of an amino acid; and (10) modulating protein-protein interactions with PI3Kgamma comprising modifying the surfaces of the B-helices.

BIOTECHNOLOGY - Preferred Polypeptide: The polypeptide fragment of phosphoinositide 3-kinasegamma (PI3Kgamma) comprises amino acids 943-951 of the catalytic loop and amino acids 964-988 of the activation loop. The polypeptide mutein of PI3Kgamma, where the amino acids at position Lys807, Lys808, Arg947, or Lys973 are mutated, and has less than normal phospholipid binding activity. Preferred Method: In modulating phospholipid substrate binding to PI3Kgamma, modifying comprises contacting an antibody specific for the phospholipid binding domain. In modulating lipid kinase catalysis, modifying comprises contacting an antibody specific for an amino acid region comprising His968, or substituting His968 with a non-conservative amino acid. Modulating RAS activity comprises modifying Lys234, Asp238, and Lys255, or contacting an antibody specific for a peptide comprising Lys234, Asp238, and Lys255. In inhibiting the binding of PI3Kgamma to cell membranes, modifying comprises contacting the amino acid with an antibody specific for the regions mentioned above. Modulating protein-protein interactions with PI3Kgamma, where B-helices are hB1, hB1', hB2, hB2', hB3, hB4, or hB5. Modifying comprises contacting the amino acid with an antibody specific for hB1, hB1', hB2, hB2', hB3, hB4, or hB5.

ACTIVITY - Cytostatic; Anti-inflammatory; Vulnerary. No biological data given.

MECHANISM OF ACTION - None given.

USE - The phosphoinositide 3-kinasegamma (PI3Kgamma) crystals, polypeptide fragments and muteins are useful for modifying PI3Kgamma activity, including phospholipid binding, lipid kinase activity, modulating RAS activity in activating PI3Kgamma, binding of PI3Kgamma to cell membranes, or modulating protein-protein interactions with

PI3Kgamma. Modulating PI3Kgamma activities is useful for regulating cellular activities, e.g. activities involved in inflammation, repair, healing, development and differentiation. The antibodies that bind to PI3Kgamma polypeptides are useful as therapeutic, diagnostic, or commercial research tools, e.g. to quantitate the levels of PI3K polypeptide in tissues or cells, or to identify the cellular localization and/or distribution of the polypeptide. (19 pages)

L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:157832 CAPLUS
DN 136:179835
TI Crystal structure of a Ras-phosphoinositide 3-kinase (PI3K) complex and use in the design and screening of ligands capable of modulating Ras-PI3K interaction
IN Eccleston, John; Pacold, Michael; Stephens, Len; Williams, Roger
PA Medical Research Council, UK
SO PCT Int. Appl., 192 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002016427	A1	20020228	WO 2001-GB3810	20010824
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2001082335	A5	20020304	AU 2001-82335	20010824
	EP 1313764	A1	20030528	EP 2001-960948	20010824
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2003022344	A1	20030130	US 2001-974573	20011009
	US 2004018957	A1	20040129	US 2003-371617	20030221
PRAI	GB 2000-20958	A	20000824		
	US 2000-242801P	P	20001023		
	WO 2001-GB3810	W	20010824		

AB The invention relates to a **crystal** comprising **phosphoinositide 3-kinase** (PI3K) and Ras, and to the use of such crystals in modeling the Ras-PI3K interaction and in the design and/or screening of ligands capable of modulating this interaction. It is shown that Ras forms a transient complex with PI3Kγ and activates it in vitro and in vivo. To characterize the PI3K interaction with Ras, the authors have trapped a Ras·PI3Kγ complex and determined its structure by x-ray crystallog. This structure of Ras in complex with PI3Kγ shows interactions that are unique to PI3Ks, and is a good model for the interaction of PI3Kα with Ras. The conformational change that take place in PI3Kγ upon Ras binding suggest that an allosteric mechanism, in addition to membrane recruitment, may be important in the Ras-mediated activation of this class of effectors.
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:894063 CAPLUS
DN 134:189953
TI Crystal structure and functional analysis of Ras binding to its effector phosphoinositide 3-kinase γ

AU Pacold, Michael E.; Suire, Sabine; Perisic, Olga; Lara-Gonzalez, Samuel; Davis, Colin T.; Walker, Edward H.; Hawkins, Phillip T.; Stephens, Len; Eccleston, John F.; Williams, Roger L.
CS MRC Laboratory of Molecular Biology, Cambridge, CB2 2QH, UK
SO Cell (Cambridge, Massachusetts) (2000), 103(6), 931-943
CODEN: CELLB5; ISSN: 0092-8674
PB Cell Press
DT Journal
LA English
AB Ras activation of phosphoinositide 3-kinase (PI3K) is important for survival of transformed cells. We find that PI3Kγ is strongly and directly activated by H-Ras G12V in vivo or by GTPγS-loaded H-Ras in vitro. We have determined a crystal structure of a PI3Kγ/Ras·GMPPNP complex. A critical loop in the Ras binding domain positions Ras so that it uses its switch I and switch II regions to bind PI3Kγ. Mutagenesis shows that interactions with both regions are essential for binding PI3Kγ. Ras also forms a direct contact with the PI3Kγ catalytic domain. These unique Ras/PI3Kγ interactions are likely to be shared by PI3Kα. The complex with Ras shows a change in the PI3K conformation that may represent an allosteric component of Ras activation.
RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:813827 CAPLUS
DN 132:290390
TI Crystal Structure of the C-Terminal SH2 Domain of the p85α Regulatory Subunit of Phosphoinositide 3-Kinase: An SH2 Domain Mimicking its Own Substrate. [Erratum to document cited in CA132:1637]
AU Hoedemaeker, Flip J.; Siegal, Gregg; Roe, S. Mark; Driscoll, Paul C.; Abrahams, Jan Pieter
CS Leiden Institute Chem. Gorlaeus Laboratoria, Universiteit Leiden, Leiden, 2300 RA, Neth.
SO Journal of Molecular Biology (1999), 294(4), 825
CODEN: JMOBAK; ISSN: 0022-2836
PB Academic Press
DT Journal
LA English
AB The legends to Figure 4(b) and Figure 4(c) were switched; the corrected figures and their legends are given. (c) 1999 Academic Press.

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:790863 CAPLUS
DN 132:90015
TI Structural insights into phosphoinositide 3-kinase catalysis and signalling
AU Walker, Edward H.; Perisic, Olga; Ried, Christian; Stephens, Len; Williams, Roger L.
CS MRC Laboratory of Molecular Biology, MRC Centre, Cambridge, CB2 2QH, UK
SO Nature (London) (1999), 402(6759), 313-320
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
AB Phosphoinositide 3-kinases (PI3Ks) are ubiquitous lipid kinases that function both as signal transducers downstream of cell-surface receptors and in constitutive intracellular membrane and protein trafficking pathways. All PI3Ks are dual-specificity enzymes with a lipid kinase activity which phosphorylates phosphoinositides at the 3-hydroxyl, and a protein kinase activity. The products of PI3K-catalyzed reactions, phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P3), PtdIns(3,4)P2 and PtdIns(3)P, are second messengers in a variety of signal transduction pathways, including those essential to cell proliferation, adhesion,

survival, cytoskeletal rearrangement and vesicle trafficking. Here we report the 2.2Å X-ray crystallog. structure of the catalytic subunit of PI3Kγ, the class I enzyme that is activated by hetero-trimeric G-protein βγ subunits and Ras. PI3Kγ has a modular organization centered around a helical-domain spine, with C2 and catalytic domains positioned to interact with phospholipid membranes, and a Ras-binding domain placed against the catalytic domain where it could drive allosteric activation of the enzyme.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:664912 CAPLUS
DN 132:1637
TI Crystal Structure of the C-Terminal SH2 Domain of the p85α Regulatory Subunit of Phosphoinositide 3-Kinase: An SH2 Domain Mimicking its Own Substrate
AU Hoedemaeker, Flip J.; Siegal, Gregg; Roe, S. Mark; Driscoll, Paul C.; Abrahams, Jan Pieter
CS Leiden Institute for Chemistry Gorlaeus Laboratoria, Universiteit Leiden, Leiden, 2300 RA, Neth.
SO Journal of Molecular Biology (1999), 292(4), 763-770
CODEN: JMOBAK; ISSN: 0022-2836
PB Academic Press
DT Journal
LA English
AB The binding properties of Src homol.-2 (SH2) domains to phosphotyrosine (pY)-containing peptides have been studied in recent years with the elucidation of a large number of crystal and solution structures. Taken together, these structures suggest a general mode of binding of pY-containing peptides, explain the specificities of different SH2 domains, and may be used to design inhibitors of pY binding by SH2 domain-containing proteins. We now report the crystal structure to 1.8 Å resolution of the C-terminal SH2 domain (C-SH2) of the P85α regulatory subunit of phosphoinositide 3-kinase (PI3 K). Surprisingly, the carboxylate group of Asp2 from a neighboring mol. occupies the phosphotyrosine binding site and interacts with Arg18 (αA2) and Arg36 (βB5), in a similar manner to the phosphotyrosine-protein interactions seen in structures of other SH2 domains complexed with pY peptides. It is the first example of a non-phosphate-containing, non-aromatic mimetic of phosphotyrosine binding to SH2 domains, and this could have implications for the design of substrate analogs and inhibitors. Overall, the crystal structure closely resembles the solution structure, but a number of loops which demonstrate mobility in solution are well defined by the crystal packing. C-SH2 has adopted a binding conformation reminiscent of the ligand bound N-terminal SH2 domain of PI3K, apparently induced by the substrate mimicking of a neighboring mol. in the crystal. (c) 1999 Academic Press.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 7 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
AN ABU09753 protein DGENE
TI New **phosphoinositide 3-kinase** gamma (PI3K gamma) **crystals**, polypeptide fragments and muteins, useful for modifying PI3K gamma activity, e.g. for regulating cellular activities involved in inflammation, repair, or healing -
IN Williams R; Ried C; Walker E H; Stephens L
PA (WILL-I) WILLIAMS R.
(RIED-I) RIED C.
(WALK-I) WALKER E H.
(STEP-I) STEPHENS L.
PI US 2003022344 A1 20030130 19p
AI US 2001-974573 20011009

PRAI US 2000-242801P 20001023
DT Patent
LA English
OS 2003-416991 [39]
DESC Human phosphoinositide 3-kinase gamma (PI3Kgamma).
AB The invention describes a **phosphoinositide 3-kinase** gamma **crystal**. The phosphoinositide 3-kinasegamma (PI3Kgamma) crystals, polypeptide fragments and muteins are useful for modifying PI3Kgamma activity, including phospholipid binding, lipid kinase activity, modulating RAS activity in activating PI3Kgamma, binding of PI3Kgamma to cell membranes, or modulating protein-protein interactions with PI3Kgamma. Modulating PI3Kgamma activities is useful for regulating cellular activities, e.g. activities involved in inflammation, repair, healing, development and differentiation. The antibodies that bind to PI3Kgamma polypeptides are useful as therapeutic, diagnostic, or commercial research tools, e.g. to quantitate the levels of PI3K polypeptide in tissues or cells, or to identify the cellular localisation and/or distribution of the polypeptide. This is the amino acid sequence of human phosphoinositide 3-kinase gamma (PI3Kgamma) used to create the crystals of the invention.

=>
<--

```
=> s (phosphatidylinositol (w) 3 (w) kinase) (5A) crystal
  20 FILES SEARCHED...
  35 FILES SEARCHED...
  56 FILES SEARCHED...
  69 FILES SEARCHED...
  95 FILES SEARCHED...
L1          29 (PHOSPHATIDYLINOSITOL (W) 3 (W) KINASE) (5A) CRYSTAL

=> duplicate
ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove
ENTER L# LIST OR (END):l1
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, BIOCOMMERCE, DGENE,
DRUGMONOG2, IMSRESEARCH, FEDRIP, FOREGE, GENBANK, IMSPRODUCT, KOSMET,
MEDICONF, NUTRACEUT, PCTGEN, PHAR, PHARMAML, RDISCLOSURE, SYNTHLINE, CHEMLIST,
HSDB, MSDS-CCOHS, MSDS-OHS, RTECS, CONF, IMSDRUGCONF, DIOGENES, INVESTEXT,
USAN, FORIS, FORKAT, UFORDAT, AQUIRE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
DUPLICATE PREFERENCE IS 'BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, EMBASE, ESBIOBASE,
MEDLINE, PASCAL, SCISEARCH, TOXCENTER'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L1
L2            7 DUPLICATE REMOVE L1 (22 DUPLICATES REMOVED)

=> s l2 NOT (complete genome)
  14 FILES SEARCHED...
  35 FILES SEARCHED...
  57 FILES SEARCHED...
  84 FILES SEARCHED...
L3            7 L2 NOT (COMPLETE GENOME)

=> d l3 1-7 bib ab

L3   ANSWER 1 OF 7  BIOSIS  COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN   2000:48668  BIOSIS
DN   PREV200000048668
TI   Selective inhibition of protein kinase C, mitogen-activated protein
     kinase, and neutrophil activation in response to calcium pyrophosphate
     dihydrate crystals, formyl-methionyl-leucyl-phenylalanine, and phorbol
     ester by O-(Chloroacetyl-carbamoyl) fumagillol (AGM-1470; TNP-470).
AU   Tudan, Christopher; Jackson, John K.; Pelech, Steven L.; Attardo, Giorgio;
     Burt, Helen [Reprint author]
CS   Faculty of Pharmaceutical Sciences, University of British Columbia, 2146
     East Mall, Vancouver, BC, Canada
SO   Biochemical Pharmacology, (Dec. 15, 1999) Vol. 58, No. 12, pp. 1869-1880.
     print.
     CODEN: BCPCA6. ISSN: 0006-2952.
DT   Article
LA   English
ED   Entered STN: 3 Feb 2000
     Last Updated on STN: 31 Dec 2001
AB   The effect of O-(chloroacetyl-carbamoyl) fumagillol (AGM-1470; TNP-470)
     was investigated on protein kinase C (PKC) and mitogen-activated protein
     kinase (MAPK) activation in neutrophils stimulated by plasma-opsonized
     crystals of calcium pyrophosphate dihydrate (triclinic) (CPPD(T)),
     formyl-Met-Leu-Phe (fMLP), and phorbol 12-myristate 13-acetate (PMA).
     Neutrophil respiratory burst responses also were determined in
     AGM-1470-pretreated cells stimulated with the same agonists, using
     chemiluminescence and superoxide anion generation assays.  AGM-1470 (5
     muM) effectively inhibited PKC activation in cells treated with CPPD(T)
     crystals (50 mg/mL, 2 min) and fMLP (1 muM, 1 min), but had no effect on
     PMA-treated cells (0.5 muM, 5 min).  AGM-1470 blocked MAPK activity
     completely and reduced neutrophil activation induced by fMLP and PMA but
     not by CPPD(T).  The degree of inhibition of the respiratory burst
```

plateaued at approximately 46 +- 9 and 54 +- 3% in fMLP- and PMA-treated cells, respectively. These data indicate that activation of neutrophil respiratory burst activity may be mediated through the MAPK pathway. AGM-1470 pretreatment did not inhibit CPPD(T) **crystal**- or fMLP-stimulated **phosphatidylinositol 3-kinase** (PI 3-kinase) activity. These findings, coupled with further observations that the PI 3-kinase inhibitor wortmannin (10 nM) inhibited fMLP- and CPPD(T) crystal-induced but not PMA-induced chemiluminescence, indicate that at least two distinct signaling pathways (mediated by PI 3-kinase or MAPK) lead to neutrophil respiratory burst responses. PKC may also be required in the MAPK-stimulated pathway. We propose that the inhibitory effect of AGM-1470 on the neutrophil respiratory burst may be due to its ability to inhibit PKC and MAPK activation.

L3 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:257653 BIOSIS
DN PREV199800257653
TI Activation of S6 kinase in human neutrophils by calcium pyrophosphate dihydrate **crystals**: Protein kinase C-dependent and **phosphatidylinositol-3-kinase**-independent pathways.
AU Tudan, Christopher; Jackson, John K.; Charlton, Lorin; Pelech, Steven L.; Sahl, Bill; Burt, Helen M. [Reprint author]
CS Dep. Med., Univ. British Columbia, Biomed. Res. Cent., Kinetek Biotechnol. Corporation, Suite 500, 520 West 6th Ave., Vancouver, BC V5Z 1A1, Canada
SO Biochemical Journal, (April 15, 1998) Vol. 331, No. 2, pp. 531-537. print. ISSN: 0264-6021.
DT Article
LA English
ED Entered STN: 9 Jun 1998
Last Updated on STN: 12 Aug 1998
AB Phosphatidylinositol 3-kinase (PI 3-kinase) has been shown previously to be a central enzyme in crystal-induced neutrophil activation. Since activation of the 70 kDa S6 kinase (p70S6K) has been shown to be dependent on PI 3-kinase activation in mammalian cells, and since the former is a key enzyme in the transmission of signals to the cell nucleus, activation of p70S6K was investigated in crystal-stimulated neutrophils. Cytosolic fractions from calcium pyrophosphate dihydrate (CPPD)-crystal activated neutrophils were separated by Mono Q chromatography and analysed for phosphotransferase activity using a range of substrates and probed by Western analysis using antibodies to p70S6K and mitogen-activated protein kinase (MAP kinase). CPPD crystals induced a robust, transient activation (peak activity at 2 min) of p70S6K that was fully inhibited by pretreatment with rapamycin. This is the first report of the activation of p70S6K in neutrophil signal transduction pathways induced by an agonist. This crystal-induced activation of p70S6K could also be inhibited by a protein kinase C (PKC) inhibitor (Compound 3), but not by the PI 3-kinase inhibitor wortmannin. CPPD crystals also activated the ERK1 and ERK2 forms of MAP kinase (wortmannin insensitive), PKC (Compound 3 sensitive) and protein kinase B (wortmannin sensitive) in neutrophils. These data suggest that activation of p70S6K may proceed through a PI 3-kinase- and protein kinase B-independent but PKC-dependent pathway in crystal-activated neutrophils.

L3 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:250344 BIOSIS
DN PREV199799549547
TI The involvement of **phosphatidylinositol 3-kinase** in **crystal** induced human neutrophil activation.
AU Jackson, John K.; Lauener, Ron; Duronio, Vincent; Burt, Helen M. [Reprint author]
CS Faculty Pharmaceutical Sci., Univ. BC, 2146 East Mall, Vancouver, BC V6T 1Z3, Canada
SO Journal of Rheumatology, (1997) Vol. 24, No. 2, pp. 341-348.

CODEN: JRHUA9. ISSN: 0315-162X.
DT Article
LA English
ED Entered STN: 13 Jun 1997
Last Updated on STN: 13 Jun 1997
AB Objective. We investigated whether phosphatidylinositol (PI) 3-kinase is involved in the signal transduction pathway leading to neutrophil activation by inflammatory microcrystals. Methods. Neutrophil chemiluminescence and degranulation responses to opsonized crystals were measured in the presence of selective inhibitors known to inhibit PI 3-kinase activity in neutrophils. Results. Wortmannin and LY 294002, 2 selective inhibitors of PI 3-kinase, were shown to inhibit neutrophil activation induced by plasma opsonized crystals of calcium pyrophosphate dihydrate (CPPD) (both monoclinic (M) and triclinic (T) forms) and monosodium urate monohydrate (MSUM). IC-50 for wortmannin or LY 294002 inhibition of crystal induced respiratory burst (measured by chemiluminescence) was about 3 nM and 0.3 mu-M, respectively, proving the pivotal role of PI 3-kinase in neutrophil respiratory burst activation by all 3 crystals. Degranulation responses of neutrophils to CPPD(M) and CPPD(T) crystals were also inhibited by about 50% by wortmannin in the 10 to 20 nM concentration range, supporting the direct involvement of PI 3-kinase in signal transduction pathways leading to crystal induced neutrophil degranulation. All 3 crystals induced the activation of PI 3-kinase in neutrophils as measured by the increased PI 3-kinase activity associated with immunoprecipitated tyrosine phosphorylated proteins from 1 min crystal-neutrophil incubations. Neutrophils pretreated with wortmannin at 10 nM showed sub-basal levels of PI 3-kinase activity at all time points measured. Conclusion. PI 3-kinase plays a central role in the signal transduction pathways leading to respiratory burst and degranulation responses in neutrophils activated by inflammatory microcrystals.

L3 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:25227 CAPLUS
DN 130:208371
TI Molecular mechanism of basic calcium phosphate crystal-induced activation of human fibroblasts. Role of nuclear factor κB, activator protein 1, and protein kinase C
AU McCarthy, Geraldine M.; Augustine, James A.; Baldwin, Albert S.; Christopherson, Pamela A.; Cheung, Herman S.; Westfall, Pamela R.; Scheinman, Robert I.
CS Dept. of Clinical Pharmacology, The Royal College of Surgeons in Ireland, Dublin, 2, Ire.
SO Journal of Biological Chemistry (1998), 273(52), 35161-35169
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Synovial fluid basic calcium phosphate (BCP) crystals are markers of severe joint degeneration in osteoarthritis. BCP crystals cause mitogenesis of articular cells and stimulate matrix metalloprotease production, thus promoting degradation of articular tissues. Previous work suggested that BCP crystal-induced cell activation required intracellular crystal dissoln., induction of proto-oncogene expression, and activation of signal transduction pathways involving protein kinase C and mitogen-activated protein kinases. Here the authors further elucidate the mechanisms of BCP crystal-induced cell activation as BCP crystals activate transcription factors nuclear factor κB and activator protein 1 in human fibroblasts. The authors confirm the role of protein kinase C in BCP crystal-induced mitogenesis in human fibroblasts. In contrast, the authors demonstrate that BCP crystals do not activate signal transduction pathways involving protein tyrosine kinases or phosphatidylinositol 3-kinase. These data further define the mechanism of cell activation by BCP crystals and confirm its selectivity, an observation that may have

therapeutic implications.
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:746724 CAPLUS
DN 126:28526
TI Crystal structure of the breakpoint cluster region-homology domain from phosphoinositide 3-kinase p85α subunit
AU Musacchio, Andrea; Cantley, Lewis C.; Harrison, Stephen C.
CS Lab. Mol. Med., Howard Hughes Med. Inst., Child. Hosp., Boston, MA, 02115, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1996), 93(25), 14373-14378
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Proteins, such as the product of the breakpoint cluster region, chimaerin, and Src homol. 3-binding protein 3BP1, are GTPase activating proteins (GAPs) for members of the rho subfamily of small GTP-binding proteins (G proteins or GTPases). A 200-residue region, named the breakpoint cluster region-homol. (BH) domain, is responsible for the GAP activity. Here, the authors describe the crystal structure of the BH domain from the p85 subunit of phosphatidylinositol 3-kinase at 2.0 Å resolution The domain was composed of 7 helixes, having a previously unobsd. arrangement. A core of 4 helixes contained most residues that were conserved in the BH family. Their packing suggested the location of a G-protein binding site. This structure of a GAP-like domain for small GTP-binding proteins provides a framework for analyzing the function of this class of mols.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:223215 CAPLUS
DN 124:254514
TI Crystal structure of PI3K SH3 domain at 2.0 Å resolution
AU Liang, Jun; Chen, James K.; Schreiber, Stuart L.; Clardy, Jon
CS Dep. Chem. Baker Lab., Cornell Univ., Ithaca, NY, 14853-1301, USA
SO Journal of Molecular Biology (1996), 257(3), 632-43
CODEN: JMOBAK; ISSN: 0022-2836
PB Academic
DT Journal
LA English
AB The human phosphatidylinositol 3-kinase (PI3K) SH3 domain, residues 1-85 of the PI3K p85 subunit, was characterized by x-ray diffraction. Crystals belonging to space group P43212 diffracted to 2.0 Å resolution and the structure was phased by single isomorphous replacement and anomalous scattering (SIRAS). As expected, the domain was a compact β barrel with an overall conformation very similar to the independently determined NMR structures. The x-ray structure illuminated a discrepancy between the 2 NMR structures on the conformation of the loop region unique to the PI3K SH3 domain. Furthermore, the ligand binding pockets of the PI3K SH3 domain were occupied by amino acid residues from sym.-related PI3K SH3 mols.: the C-terminal residues I(82) SPP of one and R18 of another. The interaction modes clearly resembled those observed for the PI3K SH3 domain complexed with the synthetic peptide, RLP1, a class 1 ligand, although there were significant differences. The solid-state interactions suggested a model of protein-protein aggregation that could be mediated by SH3 domains.

L3 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:212469 CAPLUS
DN 124:283038

TI Crystal structure of the PI 3-kinase p85 amino-terminal SH2 domain and its phosphopeptide complexes

AU Nolte, R. T.; Eck, M. J.; Schlessinger, J.; Shoelson, S. E.; Harrison, S. C.

CS Howard Hughes Medical Inst., Children's Hosp., Boston, MA, 02115, USA

SO Nature Structural Biology (1996), 3(4), 364-74
CODEN: NSBIEW; ISSN: 1072-8368

PB Nature Publishing Co.

DT Journal

LA English

AB Crystal structures of the amino-terminal SH2 domain of the p85α subunit of phosphatidylinositol (PI) 3-kinase, alone and in complex with phosphopeptides bearing pTyr-Met/Val-Xaa-Met motifs, show that phosphopeptides bind in the two-pronged manner seen in high-affinity Lck and Src SH2 complexes, with conserved interactions between the domain and the peptide sement from phosphotyrosine to Met+3. Peptide binding requires the rearrangement of a tyrosyl side chain in the BG loop to create the hydrophobic Met+3 binding pocket. The structures suggest a mechanism for the biol. specificity exhibited by PI 3-kinase in its interactions with phosphoprotein partners.

=>
<------User Break------>

=>